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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/413,110	UNGER, EVAN C.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *116-131,138-141,146-151,160,164-166,168-174 and 178-267* is/are pending in the application.

4a) Of the above claim(s) *180-225* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *116-131,138-141,146-151,160,164-166,168-174,178,179 and 226-267* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment and remarks submitted on February 16, 2007. Claims 116-131, 138-141, 146-151, 160, 164-166, 168-174 and 178-267 are pending in the application, with claims 180-225 being withdrawn as drawn to a non-elected invention. Accordingly, claims 116-131, 138-141, 146-151, 160, 164-166, 168-174, 178-179 and 226-267 are being examined on the merits herein.

The rejection of claims 116-131, 138-141, 146-151, 160, 164-166, 168-174 and 178-179 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is being withdrawn in view of Applicant's amendments to the claims to delete the impermissible new matter. However, newly examined claim 226 and the claims depending therefrom are being rejected under 35 U.S.C. 112, first paragraph, for having similar impermissible new matter.

The terminal disclaimer filed on February 16, 2007 disclaiming the terminal portion of any patent granted on this application that would extend beyond the expiration date of U.S. Patent Nos. 6,576,220, 6,716,412 and any patent granted on currently pending U.S. Patent Application Serial No. 10/865,972, has been reviewed and is accepted. The terminal disclaimer has been recorded. Accordingly the obviousness-type double patenting rejections made over these references are being withdrawn.

The rejections of claims 126-128 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,695,460 to Siegel et al, in view of U.S. Patent No. 5,334,381 to Unger and U.S. Patent No. 5,648,098 to Porter, and further in view of U.S. Patent No. 5,542,935 to Unger et al (hereinafter Unger et al. '935), is being withdrawn in view of Applicant's statement that the Unger et al. '935 patent and the subject matter of the instant application were commonly owned at the time the invention was made (see page 26 of Remarks submitted February 16, 2007.) Claims 126-128 are supported by the prior applications to which the instant applications claim priority, and thus the Unger et al. '935 patent qualifies as prior art only under the provisions of 35 U.S.C. 102(e). Accordingly, Applicant's statement of common ownership at the time of the invention is sufficient to remove the Unger et al. '935 patent as prior art under the provisions of 35 U.S.C. 103(c).

Applicant's arguments regarding the rejections of the remaining claims over U.S. Patent No. 5,695,460 to Siegel et al, in view of U.S. Patent No. 5,334,381 to Unger and U.S. Patent No. 5,648,098 to Porter have been fully considered but have not been found persuasive. The claims are being rejected as set forth below.

Election/Restrictions

The Examiner notes that the claims are being examined to the extent they read on the elected species of bioactive agent that are thrombolytic agents, as elected by Applicants on May 7, 2001, as well as the elected species of gas or gaseous precursor that is perfluorobutane, vesicles comprising phospholipids, target tissue that comprises an area of reduced blood perfusion, and a rate of administration that is from $1X10^6$ to about $8X10^6$ vesicles/Kg-sec, as elected in the same response.

The Examiner acknowledges and agrees with Applicant's argument that previously withdrawn claims 226-250 are not patentably distinct from the claims of the elected group. Accordingly, the restriction between these claims and those previously examined is being withdrawn, and claims 226-250 are being examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 226-250 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. In particular, the specification as originally filed does not specifically disclose "delivery of said bioactive agent from the vasculature through the vessel wall and into said selected tissue" enhanced by "applying to the patient ultrasonic energy," as recited in claim 226.

The specification discloses for example that "vesicles may be ruptured using ultrasound to release the bioactive agent in the region" (see page 87), and discloses a specific method of treating a tumor in which vesicles and a Carmustine are intravenously supplied, followed by ultrasonic energy application, in which it is disclosed that "the patient will receive enhanced delivery of the drug into the tumor tissue due to cavitation enhanced drug permeation caused by interaction of the ultrasound with the gas filled vesicles" (see page 97.) Thus, the specification teaches that bioactive agent, in general can be delivered by cavitation of drug-containing vesicles, and also teaches that permeation of an anti-tumor drug in tissue can be improved by applying ultrasound.

However, the specification does not teach that the cavitation of the vesicles or the application of ultrasonic energy is itself responsible for the delivery of the bioactive agent from the vasculature and into said selective tissue, or that such energy application/cavitation itself causes transport through the vessel wall, as recited in the claim. In contrast, the specification only teaches the ability of the vesicles to delivery a drug upon cavitation (i.e., the vesicles break open with ultrasonic energy and release

the drug), or to increase permeation of a drug in tissue, such as to increase the permeation of a drug deeper into tissue in which the drug has already penetrated. The specification is silent on the ability of ultrasonic energy/cavitation to affect the transport of drugs through a vessel wall or to specifically cause the transport of a drug into tissue from vasculature. Accordingly, the claim 226 recites impermissible new matter in the application, and is rejected under 35 U.S.C. 112, first paragraph. Claims 227-250 are rejected as being dependent upon claims having new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 116-125, 129-131, 138-141, 146-151, 160, 164-166, 168-174, 178-179, 226-230 and 232-250 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,695,460 to Siegel et al, issued December 9, 1997, in view of U.S. Patent No. 5,334,381 to Evan C. Unger, issued August 2, 1994, and further in view of U.S. Patent No. 5,648,098 to Thomas R. Porter, issued July 15, 1987.

Siegel et al. teaches a method that utilizes a combination of ultrasonic agent and echo contrast agent containing microbubbles, for substantially dissolving blood clots or other vascular obstructions (see abstract, in particular.) Siegel et al. teaches that the application of the ultrasonic energy to the microbubble is capable of dissolving arterial thrombi (see column 1, line 65 through column 2, line 8, in particular.) Siegel et al. teaches that a thrombolytic agent can be introduced proximate the thrombosis to further enhance the clot dissolution (see column 2, lines 1-18, in particular), and thus teaches administering a bioactive agent corresponding to the elected species of thrombolytic agent to said patient, as recited in part (i) of claims 116, 164, 226 and 251. Siegel et al. teaches that the contrast agent, such as the microbubbles, can be injected into an occluded vessel, and thus teaches the intravascular infusion of a vesicle/acoustically active composition into the patient, as recited in part (ii) of claims 116, 164 and 226.

Siegel et al. teaches that the echo contrast agent can be, for example, a dodecafluoropentane colloidal dispersion (see column 2, lines 44-47, in particular), and further teaches that various types of microbubble media may be used for the echo contrast agent, including gas filled liposomes, gas filled lipid bilayers, gas-filled microspheres, etc (see column 5, lines 30-50, in particular.) Siegel et al. teaches a preferred contrast agents are Echogen and sonicated human serum albumin (see column 5, line 50-55, in particular.) Thus, Siegel et al. teaches administering the vesicles as recited in claims 116 and 226 and the acoustically active composition, as recited in claim 164.

Siegel et al. teaches that the ultrasonic energy is applied to the microbubbles, increased cavitation of the vascular fluid surrounding the thrombosis is achieved, thus reducing or removing the thrombosis (see column 5, line 55 though column 6, line 4, in particular.) Accordingly, Siegel et al. teaches applying to the patient an ultrasonic energy to activate and/or cavitate and/or rupture the vesicles, as recited in part (iii) of claims 116, 164 and 226. Siegel et al. teaches that a suitable frequency of the ultrasonic energy may be from 25 and up to 100 kHz (see column 5, lines 29-40, in particular.) Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the frequency of the ultrasonic radiation applied to the patient, according to the guidance provided by Siegel et al, to achieve the desired therapeutic effects, such as the desired dissolution of the thrombi. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

The Examiner furthermore notes that the range of ultrasonic energy frequencies taught by Siegel et al. fails within the range that is disclosed by Applicants on page 68 of the instant specification (0.025 to 100 MHz) as being suitable for the cavitation/rupturing of the vesicles, and thus it is considered that the frequency of Siegel et al. also necessarily causes the cavitation/rupturing of the microbubbles.

Siegel et al. does not specifically teach a method in which the vesicles comprise the elected species of lipid that is phospholipids and elected species of gas that is perfluorobutane. Siegel et al. also does not specifically teach applying the recited ultrasonic frequency of between about 750 kHz and 3 MHz, as recited in claims 116, 164 and 226.

Unger teaches liposomes suitable as ultrasound contrast agents having liposomes encapsulated therein (see abstract, in particular), and thus teaches gas-filled liposomes. Unger teaches that suitable contrast agent can comprise liposomes formed from lipids such as phosphatidylcholine, phosphatidylethanolamine, etc (see column 9, lines 15-40, in particular), and thus teaches providing lipids corresponding to the elected species of phospholipids to form the gas filled liposomes. Unger also teaches that examples of suitable lipids include dipalmitoylphosphatidylcholine (see column 10, lines 15-30, in particular), and thus teaches providing the specific phospholipids as recited in claim 226.

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the phospholipid-containing liposomes of Unger in the composition and method of Siegel et al, because Siegel teaches that the composition can comprise ultrasound echo contrast agents comprising gas-filled liposomes, and teaches administering the contrast agents to reduce and

remove thrombi, and Unger teaches that gas-filled liposomes can be formed from phospholipids to provide ultrasound contrast agents. Thus, one of ordinary skill in the art would have been motivated to provide gas-filled phospholipid liposomal contrast agents in the composition and method of Siegel et al, with the expectation of providing a suitable ultrasound contrast agent capable of use in the reduction and removal of thrombi.

Siegel et al. and Unger do not specifically teach a method in which the vesicles comprise the elected species of gas that is perfluorobutane. Siegel et al. and Unger also does not specifically teach applying the recited ultrasonic frequency of between about 750 kHz and 3 MHz, as recited in claims 116, 164 and 226, or the specific elected species of administration rate.

Porter teaches a microbubble preparation and thrombolytic therapy therewith, in which the microbubbles are intravenously injected and are caused to cavitate by the application of an applied ultrasound field in the vicinity of the thrombus, thereby removing the clot (see abstract, in particular.) Thus, Porter teaches cavitating and/or rupturing microbubbles via application of ultrasound energy in the vicinity of a thrombus to provide thrombolytic effects. Porter teaches that the microbubbles can contain an internal atmosphere, such as a fluorocarbon gas, including perfluorobutane (see abstract, column 2, lines 20-35 and column 3, lines 20-35, in particular), and thus

teaches providing microbubbles having the elected species of gas that is perfluorobutane.

Porter teaches that a desired ultrasonic energy to achieve the cavitation can be as little as 20 KHz to several MHz, such as from 3 to 5 MHz (see column 4, lines 45-50, in particular), and thus teaches a frequency range that overlaps as claimed. Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the frequency of the ultrasonic radiation applied to the patient, according to the guidance provided by Siegel et al. and Porter, to achieve the desired therapeutic effects, such as the desired dissolution of the thrombi. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Regarding the elected species of rate of vesicle administration, Porter teaches that an anti thrombosis therapy can comprise administering from 0.0025 to 0.1 mg/kg of therapeutic composition over about 1 to 25 minutes (see Example 2, in particular), where the microbubble concentration may be between 0.8×10^9 and 1.5×10^9 per each milliliter (see column 6, lines 33-36, in particular.) Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the rate of delivery of the treatment agent, according to

the guidance provided by Siegel et al, Unger and Porter, to achieve the desired therapeutic effects. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to apply the ultrasonic frequencies of Porter in the method of Siegel et al. and Unger, because Siegel et al. teaches applying ultrasonic energy to the microbubbles to increase cavitation and remove or reduce the thrombus, whereas Porter teaches frequencies of ultrasonic energy that are suitable for achieving cavitation and the lysis of thrombi. Thus, one of ordinary skill in the art would have been motivated to apply the frequencies of Porter in the method of Siegel et al. and Porter, with the expectation of achieving a reduction and/or removal of the thrombus.

It is furthermore considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the perflurobutane gas of Porter in the composition and method of Siegel et al. and Unger, and to administer the composition at the rate taught by Porter, because Siegel et al. and Unger teach that the composition can comprise gas filled microbubbles, such as gas-filled liposomes, and teach administering the microbubbles to reduce and remove thrombi, and Porter

teaches that perfluorobutane is a gas suitable for microbubble cavitation treatment of thrombi, and teaches rates of therapeutic composition delivery that are suitable for the reduction and/or removal of the thrombi. Thus, one of ordinary skill in the art would have been motivated to provide the perfluorobutane in the gas-filled microbubbles/liposomes of Siegel et al. and Unger, and to administer the microbubbles at the rate taught and/or rendered obvious by Porter, with the expectation of providing microbubbles and a microbubble administration rate capable of being ultrasonically cavitated to reduce and/or remove thrombi.

Regarding the recitation that the method is "for the delivery of a bioactive agent from the vasculature to a selected tissue in a patient" as recited in claims 116 and 164, or "for enhancing" such delivery as in claim 226, it is noted that the recitation of an intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963.) Thus the intended use recited in claims 116, 164 and 226, namely that the method is for "the delivery of a bioactive agent from the vasculature to a selected tissue in a patient," or the enhancement thereof, is not afforded patentable weight.

Regarding the recitation of "delivering said bioactive agent from the vasculature through the vessel wall and into said selected tissue by cavitation and/or rupturing said vesicles" as in claim 116, or "by activating said acoustically active composition" as in claim 164, or "applying to the patient ultrasonic energy ... to thereby enhance delivery of said bioactive agent," as in claim 226, it is noted that as Siegel et al, Unger and Porter render obvious the same method steps as instantly claimed, namely the delivery of active agents and microbubbles and the application of ultrasonic energy in the frequency range to rupture and/or cavitate the microbubbles to remove thrombi, it is considered that the method necessarily also causes the delivery of the bioactive agent from the vasculature into the tissue of the patient. It is respectfully pointed out that a recitation of an intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. In a claim drawn to a process, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963.) Thus the intended use recited in claims 116, 164 and 226, namely that the application of ultrasonic energy causes the delivery of the bioactive agent into the tissue, is considered to be taught by the combination of Siegel et al, Unger and Porter.

Accordingly, claims 116, 164 and 226 are obvious over the teachings of Siegel et al, Unger and Porter.

Regarding claims 117, 165 and 227, Porter teaches infusion over 1-25 minutes (see column 7, lines 60-66, in particular), and thus is considered to teach continuous infusion, as recited in the claims. Regarding claims 118, 166 and 228, Siegel et al. teaches that a combination of echo contrast agent (e.g. microbubbles) and thrombolytic agent or disruptive agent can be injected proximate a thrombosis disposed in a vessel in the body (see column 3, lines 14-20, in particular), and thus is considered to teach administration of the vesicle composition and thrombolytic agent substantially simultaneously, as recited in the claims. Regarding claims 119, 173 and 229, Siegel et al. teaches that it is known to use ultrasonic imaging to locate and image intravascular thrombi (see column 1, lines 10-20, in particular), and thus it is considered that it would be obvious to combine ultrasonic imaging with the method taught therein to image the thrombi before and/or after treatment.

Regarding claims 120-123, Unger teaches that the ultrasound imaging vesicles can be formed of liposomes containing phospholipids such as phosphatidylcholine, phosphatidylethanolamine, etc (see column 9, lines 15-40, in particular.) Regarding claims 124-125 and 230, Unger teaches providing dipalmitoylphosphatidylcholine (see column 10, lines 20-30, in particular.) Regarding claims 129-131, Unger teaches that the surface of the liposome can be modified by incorporating a polymer such as polyethylene glycol (see column 9, lines 30-40, in particular.)

Regarding claims 138-141 and 232-235, Porter renders obvious providing perfluorobutane as the gas incorporated in the liposomes, as discussed above. Regarding claims 146-151 and 236-249, the teachings of Siegel et al, Unger and Porter render obvious providing the composition at the rate corresponding to the elected species. Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the rate of administration of the composition, according to the guidance provided by Siegel et al, Unger and Porter, to provide the desired therapeutic treatment. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Regarding claims 160, 174 and 250, Siegel et al. teaches providing a thrombolytic agent, as recited in the claim.

Regarding claims 168-172, Siegel et al. teaches treating a thrombus, as discussed above, which is a blood clot that can cause reduced blood perfusion in an area as well as ischemic tissue, including in the myocardium and in glandular tissue, such as in the prostate gland. Accordingly, it would be obvious over the teachings of the references to provide treatment of tissue affected by the presence of thrombi, and including those tissue types recited in the claims.

Regarding claims 178-179, Siegel et al. teaches that the treatment composition can be administered and subsequently, the ultrasound radiation can be applied (see column 5, lines 15-25, in particular.) However, it is also noted that the apparatus of Siegel et al, as displayed in Figure 1, allows for administering the treatment agent and ultrasound application "at about the same time", as recited in the claim, and thus it is considered that one of ordinary skill in the art would have found it obvious to intravenously introduce the composition proximate to the clot and very shortly thereafter apply ultrasound such that the application occurs at "about the same time." Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of time delayed between providing the composition and applying ultrasound energy, according to the guidance provided by Siegel, Unger and Porter, to provide a desired treatment method. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Claims 126-128, 231 and 251-267 are rejected under 3 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,695,460 to Siegel et al, issued December 9, 1997, in view of U.S. Patent No. 5,334,381 to Evan C. Unger, issued August 2, 1994, and further in view of U.S. Patent No. 5,648,098 to Thomas R. Porter, issued July 15, 1987, as applied to claims 116-125, 129-131, 138-141, 146-151, 160, 164-166, 168-174, 178-

179, 226-230 and 232-250 above, and further in view of U.S. Patent No. 5,393,530 to Schneider et al, issued February 28, 1995.

Siegel et al, Unger and Porter are applied as discussed above, and teach a method of reducing thrombi by applying ultrasound energy to a contrast agent that can comprise a gas-filled liposome, such as a liposome formed from phospholipids, including phosphatidylcholine, phosphatidylethanolamine and phosphatidic acid.

The references do not specifically teach that the liposome can comprise phospholipids such as dipalmitoylphosphatidylethanolamine and/or dipalmitoylphospatidic acid, as recited in claims 126-128, 231 and 251-267.

Schneider et al. teaches liposome vesicle formulations capable of entrapping substances for drug delivery (see abstract, in particular.) Schneider et al. teaches that suitable lipids for forming such liposome vesicles include those commonly used in the liposome art, such as dipalmitoyl phosphatidic acid (DPPA) and dipalmitoyl phosphatidylethanolamine (DPPE) (see column 5, lines 30-60, in particular), and thus teaches providing the specific phospholipids as claimed to form liposome vesicles.

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the specific phospholipid-containing liposomes of Schneider in the composition and method of Siegel et al, Unger

and Porter, because Siegel et al, Unger and Porter teach that the composition can comprise ultrasound echo contrast agents comprising gas-filled liposomes, and teaches administering the contrast agents to reduce and remove thrombi, where the liposomes can be formed from phospholipids, and Schneider et al. teaches that the specific phospholipids as claimed are commonly known to be suitable for the formation of liposomes. Thus, one of ordinary skill in the art would have been motivated to provide the specific phospholipids as claimed as the lipids in the gas-filled phospholipid liposomal contrast agents in the composition and method of Siegel et al, Unger and Porter, with the expectation of providing a suitable phospholipids for forming the vesicles for the administration of ultrasound contrast agents capable of use in the reduction and removal of thrombi. Accordingly claims 126-128, 231 and 251 are obvious over the teachings of Siegel et al, Unger, Porter and Schneider et al.

Regarding claims 252-254, Schneider et al. teaches providing DPPE and DPPA, as discussed above.

Regarding claim 255, Porter teaches infusion over 1-25 minutes (see column 7, lines 60-66, in particular), and thus is considered to teach continuous infusion, as recited in the claim. Regarding claim 256, Siegel et al. teaches that a combination of echo contrast agent (e.g. microbubbles) and thrombolytic agent or disruptive agent can be injected proximate a thrombosis disposed in a vessel in the body (see column 3, lines 14-20, in particular), and thus is considered to teach administration of the vesicle

composition and thrombolytic agent substantially simultaneously, as recited in the claim. Regarding claim 257, Siegel et al. teaches that it is known to use ultrasonic imaging to locate and image intravascular thrombi (see column 1, lines 10-20, in particular), and thus it is considered that it would be obvious to combine ultrasonic imaging with the method taught therein to image the thrombi before and/or after treatment.

Regarding claims 258-261, Porter renders obvious providing perfluorobutane as the gas incorporated in the liposomes, as discussed above. Regarding claims 262-267 and 236-249, the teachings of Siegel et al, Unger and Porter render obvious providing the composition at the rate corresponding to the elected species, as discussed above. Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the rate of administration of the composition, according to the guidance provided by Siegel et al, Unger and Porter, to provide the desired therapeutic treatment. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Response to Arguments

Applicant's arguments regarding the rejections of the claims have been fully considered but they are not persuasive.

Applicant argues that the Examiner has not set forth a proper prima facie case of obviousness for the recited frequency range of from 750 kHz to 3 MHz. In particular, Applicant argues that Siegel et al. teaches a lower frequency range than that claimed, and the use of Porter's frequency range amounts to only an "obvious to try" approach, and thus does not constitute a proper prima facie case.

The Examiner respectfully disagrees. The Examiner notes that Siegel et al. is cited for teaching the general concept of providing ultrasonic energy to rupture vesicles and treat thrombi. While Siegel et al. does not specifically teach the ultrasonic frequency range as claimed, Porter teaches a general range of frequencies of from 20 KHz to several MHz, such as from 3 to 5 MHz that are considered to be suitable to achieve cavitation to rupture microbubbles (vesicles) to provide thrombolytic therapy, which ranges overlap with those claimed, as has been discussed above. Accordingly, as Porter teaches that this range is suitable, it is considered that one of ordinary skill in the art would have found it obvious to select a frequency that lies in both the range taught by Porter as well as that claimed, with the expectation of achieving rupture of the vesicles. It is furthermore noted that Porter teaches that the ultrasound signal "activates" the microbubbles to provide the rupturing and thrombolysis (see column 4, lines 40-46, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the frequency applied to increase cavitation of the vesicles, according to the

guidance provided by Siegel et al. and Porter, to provide the desired degree of "activation" and cavitation of the vesicles to aid in removal of the thrombus. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Applicants also argue that Siegel et al. teaches that the degree of dissolution of clots gets progressively worse with increasing frequency, and points out that Siegel et al. teaches that "when ultrasound is applied at a lower, rather than a higher frequency, the effectiveness of the method is markedly enhanced" (see column 5, lines 29-31 of Siegel et al.) The Examiner agrees that Siegel et al. does not teach the desirability of using higher ultrasound frequencies those within the claimed range. However, Porter teaches that frequencies overlapping with the claimed range are in fact suitable for cavitation of the vesicles to treat thrombosis, and even teaches that a preferred higher range of from about 3 to about 5 Mhz can be used, which range overlaps with the upper end of Applicant's claimed range. Accordingly, the teachings of Porter supplement those of Siegel et el. to show that higher frequencies can indeed be used for the vesicle cavitation and thrombolysis, and thus one of ordinary skill in the art would have been motivated to use the higher frequencies of Porter with the expectation of success in achieving the thrombosis treatment.

Applicant furthermore seeks to remove Porter as a prior art reference by the filing of a Declaration under 37 CFR 1.131 asserting invention prior to the effective date of

the Porter reference. This declaration filed February 16, 2007 and signed by Evan G Unger, the sole inventor of the instant application has been considered but is ineffective to remove the Porter reference as prior art.

In particular, the evidence submitted is insufficient to establish a reduction to practice of the invention in this country or a NAFTA or WTO member country prior to the effective date of the Porter reference. The declaration states that invention was conceived of in the United States and reduced to practice before the October 17, 1995 filing date of the Porter reference. However, the declaration provides no evidence of such reduction to practice that could be used to verify the asserted reduction to practice (see MPEP §715.07[R3]).

In particular, it is noted that priority of invention under 37 CFR 1.131 requires a showing of FACTS, not merely conclusions. Evidence in the form of exhibits may accompany the affidavit or declaration. Each exhibit relied upon should be specifically referred to in the affidavit or declaration, in terms of what it is relied upon to show. For example, the allegations of fact might be supported by submitting as evidence one or more of the following: (A) attached sketches; (B) attached blueprints; (C) attached photographs; (D) attached reproductions of notebook entries; (E) an accompanying model; (F) attached supporting statements by witnesses, where verbal disclosures are the evidence relied upon. Ex parte Ovshinsky, 10 USPQ2d 1075 (Bd. Pat. App. & Inter. 1989); (G) testimony given in an interference. Where interference testimony is used, the

applicant must point out which parts of the testimony are being relied on; examiners cannot be expected to search the entire interference record for the evidence. Ex parte Homan, 1905 C.D. 288 (Comm'r Pat. 1905); (H) Disclosure documents (MPEP § 1706) may be used as documentary evidence of conception. Exhibits and models must comply with the requirements of 37 CFR 1.91 to be entered into an application file. See also MPEP § 715.07(d).

A general allegation that the invention was completed prior to the date of the reference is not sufficient to establish prior invention. Ex parte Saunders, 1883 C.D. 23, 23 O.G. 1224 (Comm'r Pat. 1883). Similarly, a declaration by the inventor to the effect that his or her invention was conceived or reduced to practice prior to the reference date, without a statement of facts demonstrating the correctness of this conclusion, is insufficient to satisfy 37 CFR 1.131.

Accordingly, the declaration is deemed insufficient to remove the Porter reference as available prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMC

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